DETAILED ACTION

1. Claims 40-72 and 74-91 are pending and under consideration in this Office Action.

2. The finality of the Office Action filed 05/02/2007 has been withdrawn. New rejections and new grounds of rejection are presented in the instant Office Action.

3. A signed copy of from PTO 1449 for the IDS filed 08/16/2007 is attached to the instant Office Action.

4. Claims 82, 84, 89, and 87 are objected to under 37 CFR 1.75 as being a substantial duplicates of claim 72, 78, and 71, respectively.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 40-70, 72, 74-77, 80-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed toward the USPTO Written Description Training Materials made available to the public on 04/11/2008 for information regarding examination of patent claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph.

According to MPEP 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v.Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed.Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

The claims are genus claims encompassing a method to produce glucosamine by fermentation comprising using a genus of genes having genetic modifications such as deletion, insertion, and substitution of at least one nucleotide in the coding region encoding a bacterial or yeast glucosamine-6-phosphate synthase which results in increased glucosamine-6-phosphate synthase activity. The scope of each genus includes many nucleic acid molecules with widely differing nucleotide sequences and structures, where the genus is highly variable because a significant number of structural and biological differences between genus members exists.

While the specification and the prior art discloses bacterial and yeast glucosamine-6-phosphate synthases, the specification, however, does not describe any correlation between any structure and nucleotide sequence with the biological function of increased glucosamine-6-phosphate synthase activity. There is no art-recognized correlation between any structure and nucleotide sequence of members of the claimed genus of nucleic acid molecules and their biological function of increased glucosamine-6-phosphate synthase activity. Those of ordinary skill in the art would not be able to identify without further testing which of those genetic modifications such as deletion, insertion, and substitution of at least one nucleotide in the coding region would also result in increased glucosamine-6-phosphate synthase activity.

Vas-Cath, Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the claimed genus of genes having genetic modifications such as deletion, insertion, and substitution of at least one nucleotide in the coding region encoding a bacterial or yeast glucosamine-6-phosphate synthase which results in increased glucosamine-6-phosphate synthase activity.

7. Claim 40-70, 72, 74-77, 80-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants' arguments filed 02/13/2007 have been fully considered but they are not persuasive.

As stated in the previous Office Actions, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing the claimed modified coding region of a gene encoding glucosamine-6-phosphate synthase that has increased enzyme activity requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities, which would clearly constitute undue experimentation.

Guo et al. (Proc Natl Acad Sci U S A. 2004 Jun 22;101(25):9205-10; reference of record) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the

percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced.

Applying this estimate to the *E.coli* glucosamine-6-phosphate synthase having 100 mutation within its amino acid sequence consisting of 609 amino acid residues would result in about 9 X 10^{-20} % of random mutants having any activity. Similarly, 50 mutations only about 9 X 10^{-10} % would be active, and 25 mutations about 3 X 10^{-5} % would be active.

Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for an *E.coli* glucosamine-6-phosphate synthase having 25 mutations (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the case for an *E.coli* glucosamine-6-phosphate synthase having 50 mutations would not be possible.

The examiner maintains that since a large amount of screening is required, the specification and prior art must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided by the instant specification, the declaration of Dr. Deng filed 02/19/2002, and the declaration of Dr. Demain filed 04/21/2006. Furthermore, the specification, the declaration of Dr. Deng filed 02/19/2002, and the declaration of Dr. Demain filed 04/21/2006 do not disclose what domains and motifs within the amino acid sequence of the *E.coli* glucosamine-6-phosphate can be modified to make a glucosamine-6-pohsphate synthase that has increased activity compared to an unmodified glucosamine-6-pohsphate synthase.

Furthermore, the specification does not provide guidance, prediction, and working examples showing any correlation between any structure and nucleotide sequence with the biological function of increased glucosamine-6-phosphate synthase activity. There is no art-recognized correlation between any structure and nucleotide sequence of members of the claimed genus of nucleic acid molecules and their biological function of increased glucosamine-6-phosphate synthase activity. Those of ordinary skill in the art would not be able to identify without further testing which of those genetic modifications such as deletion, insertion, and substitution of at least one nucleotide in the coding region would also result in increased glucosamine-6-phosphate synthase activity.

The examiner maintains that general teachings for screening and searching for the glucosamine-6-phosphate synthase with the desired properties is not guidance for making the claimed invention. Without additional guidance regarding the specific type of genetic modification to perform on the specific codons within the coding region of any polynucleotide encoding glucosamine-6-phosphate synthase that lead to the desired increase in enzyme activity or decreased product inhibition, then the experimentation left to those skilled in the art is undue. The examiner's position is that the instant specification is only enabling for a method for searching and screening for mutant glucosamine-6-phosphate synthases that have the recited properties such as increased enzyme activity and reduced product inhibition.

Claim Rejections - 35 U.S.C. § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 40, 53, 55, 62-64, 71, 75, 76-79, and 87-89 are rejected under 35 U.S.C. 102(b) as being anticipated by Dutka-Malen et al. Dutka-Malen et al. reference has been attached to the previous Office Action dated (7/20/00) and is not attached to the instant Office Action.

Dutka-Malen et al. make a genetically engineered E.coli host cell (see Fig. 1, p. 288) which is transformed with a recombinant vector containing the E.coli gene encoding glucosamine-6-phosphate synthase suitably linked to a lac promoter wherein said host cell overexpresses glucosamine-6-phosphate synthase as evident by an increase in enzyme activity. Glucosamine-6-phosphate synthase catalyzes the formation of glucosamine-6-phosphate. Genetic modifications include transformation of E.coli host cells with a recombinant vector containing a nucleic acid sequence which encodes glucosamine-6-phosphate synthase and overexpression of said synthase. Furthermore, linking the nucleic acid sequence encoding glucosamine-6-phosphate synthase to said lac promoter in said recombinant vector is a mutation

to the glucosamine-6-phosphate synthase gene (glms). Dutka-Malen et al. teach a process comprising culturing the genetically engineered *E.coli* host cell in LB medium and the cells harvested by centrifugation and enzyme purification performed (see pp. 288-290).

Since the process steps taught by Dutka-Malen et al. are the same as the recited process steps, then the process would produce glucosamine and the harvesting of the cells by centrifugation would result in the recovery of the produced glucosamine in the remaining culture media. Thus, the reference teachings anticipated the claimed invention.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Thursday and alternate Fridays between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on (571)272-0934. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian L. Fronda/

Patent Examiner

Art Unit 1652